other asserted utilities, the specification expressly asserts a specific, substantial and credible utility of HPTK6 as marker for cancer. The Examiner also fails to address the Declaration of Dr. Paul Godowski, which was earlier submitted under 35 U.S.C. §1.132, wherein Dr. Godowski directs the Examiner's attention to the specification of the present application that clearly shows that HPTK6, while not expressed in adult or fetal liver, is expressed in Hep3B cells, a cell line representative of liver cancer and additionally is overexpressed in MCF-7 cells, a cell line representative of breast cancer. As Dr. Godowski states in the Declaration, "The data showing overexpression of HPTK6 in cell lines derived from two independent tumors in two distinct tissues is indicative of a role for HPTK6 in cancer and is unlikely to be a coincidence." The scientific stature of Dr. Godowski is beyond question and his Declaration should not be ignored or easily dismissed without a strong evidentiary showing. The Examiner's continued rejection simply repeats the earlier made contentions without addressing the evidence provided in Dr. Godowski's Declaration that would, to one of ordinary skill in the art, indicate the specification clearly discloses the asserted utility.

Further, the Examiner refers to earlier arguments that were not well-grounded with respect to Jones et al. Applicants respectfully reassert that no *prima facie* case of a lack of utility has been established according to the Revised Interim Utility Guidelines, and that reliance on Jones is an improper application of the "credibility" analysis according to the Guidelines.

The Examiner's continued rejection of the claims ignores the evidence of the specification, the Declaration of Dr. Godowski, the U.S. Patent Office Revised Utility Guidelines for establishing a lack of utility, and rests primarily on the Examiner's earlier stated erroneous conclusion that, "...an artisan would not accept the evidence that HPTK6 mRNA is expressed in a single breast cell line, but not breast or liver, as reasonably supporting a conclusion that HPTK6

mRNA expression is diagnostic for a specific cancer." (Office Action dated March 7, 2002, paragraph 5). From this Examiner's conclusion, the Office present office action continues to simply assert that one of ordinary skill in the art would not find that the present application discloses a utility. The Examiner has without reference to any authority extrapolated an overly broad conclusion, which serves as the foundation for maintaining this immediate rejection. This erroneous conclusion was rebutted as being overly broad and unsupported in the Declaration of Dr. Godowski but this Declaration has been ignored by the Examiner. When the Examiner takes it upon himself to make a broad statement that obviously is his personal conclusion and relies upon his conclusion as if it were a fact in maintaining a rejection, the Examiner is obligated under 35 U.S.C. 104(d)(2) to submit an affidavit attesting to that fact; an affidavit, which is subject to contradiction or explanation of the Applicants or other persons. Applicants therefore assert that an Affidavit by the Examiner attesting to and supporting his statements is required.

An express asserted utility is found on page 97, at lines 18-19 of the specification where reference is made to the results in Table 3 showing positive indication HPTK6 for liver carcinoma and that the results indicate that HPTK6 plays a role in cancer formation of certain cells. This asserted utility is specific, substantial and credible. It is clearly shown in the specification and is reaffirmed in the Declaration of Dr. Godowski. The asserted utility and supporting testing is perfectly demonstrated in that healthy liver tissue is tested as a baseline and compared with cancerous liver cells showing a positive result for HPTK6.

As before, the Applicants direct the Examiner's attention to the evidence in the specification. In Figure 10, healthy liver tissue from both an adult and a fetus are tested for the presence of HPTK6. There being no detectable HPTK6 in healthy liver tissue, this forms a qualitative baseline to test for the presence of HPTK6 in cancerous liver cells. As summarized

in Table 3, cancerous liver cells (Hep3B) tested positive for HPTK6.

Despite this express assertion and supporting tests, the Office Action continues to maintain the position that the claimed invention has no credible, specific, and substantial utility in the identification of liver cancer. The Office Action maintains this position despite the utility described and tested as shown in Figure 10 (showing a baseline of zero HPTK6 in both healthy adult and healthy fetal liver tissue) and at pages 94-97 of the specification, wherein the qualitative expression of HPTK6 mRNA in liver tissue and a cell lines representative of liver carcinoma (Hep3B cell line) are demonstrated. The expression of HPTK6 mRNA in liver carcinoma is recorded as positive in Table 3, while, as noted at page 95, lines 30-31 (referring to Figure 10) no expression of HPTK6 mRNA is recorded for healthy liver cells. This fact is attested to in Dr. Godowski's Declaration, which cannot be ignored or dismissed.

In maintaining this position, the Office Action continues to erroneously rely upon Jones et al., (*Cancer Genetics and Cytogenetics* 117: 153-158 (2000)) as purportedly providing evidence to rebut an assertion of utility with respect to diagnosis of breast cancer by the detection of HPTK6 mRNA over-expression in an MCF-7 cell line from Table 3. Applicants respectfully assert that this reliance on Jones et al. is not well placed.

First, Jones does not address the expression of HPTK6 in liver cells. Second, in relying upon Jones, the Office Action sets forth broad statements concerning MCF-7 cells. However, Jones has no data or reference with respect to HPTK6 specifically. Therefore, Jones cannot be relied upon as presenting evidence reasonably relevant to HPTK6 specifically. In support of this reasoning, Applicants earlier provided the Declaration of Dr. Godowski, a Declaration that has not been addressed by the Examiner but has still been summarily refuted by the Examiner's personal conclusion, quoted above.

Applicants point out that the Examiner's reliance on the Jones reference, in traverse to Applicants' assertion of credible utility, is overly burdensome and not within U.S. Patent Office Guidelines. The Office Action mailed March 7, 2002, at pages 2-3, states as follows:

> "One of ordinary skill in the art, however, would not accept these results as supporting a conclusion that the expression of HPTKA6 mRNA in a liver of [sic] breast sample is diagnostic for cancer simply because cell lines are not necessarily representative of the cancers from which they were derived. To illustrate this fact, the Jones et al. publication (Cancer Genetics and Cytogenetics 117: 153-158, 2000) is being cited because it shows that different MCF-7 cell stocks are known to not even be predictive of one another."

The Examiner's argument is an improper application of the "credibility" analysis according to the Revised Interim Utility Guidelines. Applicants set forth in their previous response that there is a substantial, credible, and specific utility for HPTK6, namely the detection and treatment of liver cancer by HPTK6 by using HPTK6 antibodies, antisense, etc. This utility is expressly asserted in at page 97 of the specification. According to the Revised Interim Utility Guidelines, an assertion is credible unless the logic underlying the assertion is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. By ignoring the Dr. Godowski's Declaration and substituting the Examiner's own conclusion as a basis for maintaining the rejection, the Examiner has questioned the credibility of the Applicant's assertion and proofs of utility without proper foundation.

There is no reasonable basis to doubt that the results in Table 3 of the specification logically support Applicants' assertions above. In addition, the Revised Interim Utility Guidelines Training Materials published at www.uspto.gov state specifically, on page 5, with respect to the credibility analysis that "nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. *Therefore, the credibility of such an assertion would not be questioned*" (*emphasis* added). Therefore, the burden placed on Applicants in response to

their asserted utility of HPTK6 as a cancer marker is improper as prescribed by the Revised Interim Utility Guidelines for rejections under 35 U.S.C §101 at the United States Patent and Trademark Office.

Applicants asserted utility also survives the remaining analysis in that the claimed polynucleotides can serve as diagnostic markers for the specific disease of liver cancer, and that identification or diagnosis liver cancer is a substantial "real world" application. Applicants note that there has been no substantial written analysis in any previous Office Action with respect to the utility of detecting cancer in liver cells. This asserted utility and supporting testing is fully demonstrated in that healthy liver is tested as a baseline and compared with cancerous liver cells showing a positive result for the presence of HPTK6. In Figure 10, healthy liver tissue from both an adult and fetus are tested for the presence of HPTK6. There being no detectable HPTK6 in healthy liver tissue, this forms a baseline for testing the presence of HPTK6 in cancerous liver cells. As summarized in Table 3, cancerous liver cells (Hep3B) cells tested positive for HPTK6. It is possible that the Examiner may criticize the finding that the HEP3B are a cell line, in the same way that the MCF-7 cell line was critically reviewed in the previous Office Action. In anticipation of such criticism, Applicants refer to Figure 2 in Johnson et al. already of record (and fully addressed in Applicants earlier response relating to a rejection under 35 U.S.C. §102(a) and now withdrawn). In Figure 2 of Johnson, in lane k, human HepG2 cells (another line of cancerous liver cells) also tested positive for the presence of HPTK6. This confirms, by external validation, the asserted utility in Applicants specification as a marker for cancerous liver cells. The Examiner's erroneous reliance on Jones et al. and his own conclusion ignores the evidence of the present specification, the Declaration of Dr. Godowski, and the external validation provided by Johnson et al.

Applicants respectfully summarize that they have clearly expressed a utility in their specification with respect to HPTK6 as being a marker for cancer of the liver. Two baseline measurements from separate liver tissue samples have established that HPTK6 is not detectable in healthy liver cells. In the specification, a cancerous liver cell line (Hep3B) provides a positive result for HPTK6. This result is confirmed, by external and independent evaluation, for another line of cancerous liver cells (HepG2) in Johnson. Therefore, the asserted utility is clearly demonstrated as credible and further scrutiny or criticism is wholly unjustified.

Applicants respectfully submit that the present disclosure provides a specific, substantial and credible utility for the claimed invention. Accordingly, reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §101 is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

Claims 31-44 are rejected under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to use the instant invention. Applicants respectfully traverse this rejection.

A deficiency under 35 U.S.C. §101 also creates a deficiency under 35 U.S.C. §112, first paragraph. In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967). Thus, in order to be enabled, a claim must be supported by a disclosure showing practical utility. As discussed above, the present disclosure provides a specific, substantial and credible utility for the claimed invention. Thus, the claimed invention meets the requirements of 35 U.S.C. §112, first paragraph.

Reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. §102(a)

Claims 31-33, 35-38, and 40-44 are rejected under 35 U.S.C. §102(a) as being clearly anticipated by Di Marco et al. (J. Biol. Chem. 268:24290-24295, 15 Nov. 1993). The Applicants respectful traverse this rejection.

With respect to Di Marco, the Office Action has taken the position that the current evidence of record is insufficient to swear behind the references unless the demonstrate a knowledge of an association between HPTKA6 and NGF action on keratinocytes before the publication date of Di Marco et al. This requirement by the Examiner is wholly unsupported by any legal requirement. Under In re Moore, 444 F.2d 572 (CCPA 1971) it was clearly established that in *Ex Parte* prosecution, unlike Interference practice, no showing of utility is required in a Rule 1.131 Declaration unless the reference to be overcome also discloses a utility. This proposition has been upheld in later cases such as In re Borkowski, 505 F.2d 713 (CCPA 1974). Further, and most importantly, the Applicants Declaration under 37 C.F.R. §1.131 fully supports that the claimed subject matter was in the possession of the inventors prior to the publication of Di Marco et al. Nothing more is legally required in an Ex Parte prosecution. Based upon the Applicants earlier submitted Declaration under 37 C.F.R. §1.131, Di Marco et al. is removed as a reference in the present rejection.

Di Marco is limited to characterizing the protein and conjectures as to its role as a receptor for Nerve Growth Factor. There is no asserted utility, and no comparative evidence that could even be construed to imply a utility. There is no legal requirement for the Applicants to do more than has been done in the submission of the Declaration under 37 C.F.R. §1.131 and certainly no requirement to comply with the Examiner's immediate requirement.

In view of the above, Applicants submit that the claimed invention has been established

as invented prior to the publication of Di Marco. Reconsideration and withdrawal is respectfully requested.

CONCLUSION

In light of the above, Applicants believe that this application is now in condition for allowance and therefore requests favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP

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Date

Steven B. Kelber
Registration No. 30,073
Attorney of Record

Perry E. Van Over
Registration No. 42,197

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085